Paper No. 20

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte SAIKO HOSOKAWA, TOSHIAKI TAGAWA, YOKO HIRAKAWA, NORIHIKO ITO and KAZUHIRO NAGAIKE

Appeal No. 2002-1358
Application No. 09/467,903

HEARD: March 20, 2003

Before WINTERS, MILLS, and GRIMES, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 30-49, which are the claims pending in this application.

Claims 30 and 39 are representative of the claims on appeal and read as follows:

30. A pharmaceutical composition comprising a therapeutically effective amount of a monoclonal antibody fragment bound to the surface of a liposome enclosing an anti-cancer agent or toxin to cancer cells and a pharmaceutically acceptable carrier therefor,

said liposome comprising phosphatidylcholine, cholesterol and phosphatidylethanolamine,

said liposome being modified with poly(ethylene glycol), wherein the poly(ethylene glycol) is bound to the surface of the liposome through a maleimide group,

said antibody fragment belonging to IgG class or IgM class and specifically binding to a surface antigen of a stomach and colon cancer cell membrane, and

said antibody fragment having a variable region of the heavy chain which comprises the amino acid sequence shown in SEQ ID No: 5 and having a variable region of the light chain which comprises the amino acid sequence of SEQ ID No:6.

34. The pharmaceutical composition of claim 30, wherein the monoclonal antibody fragment is a $F(ab')_2$ antibody fragment.

No prior art references are relied upon by the examiner.

The references relied upon by the appellants are:

Wright et al (Wright, "Antibody-directed liposomes as drug delivery vehicles," Advanced Drug Delivery Reviews, Vol. 3, pp. 343-389 (1989)

Singhal et al (Singhal), "Antibody-mediated targeting of liposomes to erythrocytes in whole blood," Biochimica et Biophysica Acta, Vol. 880, pp. 72-77 (1996)

Traut et al. (Traut), "Methyl 4- Mercaptobutyrimidate as a Cleavable Cross-Linking Reagent and Its Application to the Escherichia coli 30S Ribosome," Biochemistry, Vol. 12, No. 17 (1973)

Procedural Background

The original claims in the application were directed to a human monoclonal antibody and an anti-cancer formulation comprising the antibody. Appellants filed a preliminary amendment (Paper No. 2, Dec. 21, 1999), amending the claims to recite a

pharmaceutical composition comprising antibody fragments. Thus, the present claims have been limited by Appellants to a pharmaceutical composition comprising antibody fragments.

Technical Background

The claimed invention encompasses a pharmaceutical composition comprising a therapeutically effective amount of a monoclonal antibody fragment bound to the surface of a liposome enclosing an anti-cancer agent or toxin to cancer cells and a pharmaceutically acceptable carrier. The monoclonal antibody fragment is specifically defined in the claims with reference to particular variable regions of the heavy and light chains of the antibody fragments. Specification, pages 4, 7-8. Anticancer agents encapsulated in the liposome include carcinostatic agents such as adriamycin, daunomycin, mitomycin, cisplatin, vincristine, toxins such as ricin A and diphtheria toxin, and antisense RNA. Specification, page 11. The antibody portion of the pharmaceutical composition is provided to target and concentrate an anticancer agent to a tissue or organ to be treated. Specification, pages 1 and 41.

The preparation and use of Fab' fragments bound to liposome are disclosed in the specification at pages 11-12. The Fab' fragments are prepared from $F(ab')_2$

fragments.[1] The Fab' fragments are then bound to a liposome by a thiol group to a maleimide group in the liposome. Specification, page 12, 36.

Grounds of Rejection

Claims 30-49 stand rejected under 35 U.S.C. § 112, first paragraph for lack of written description and failing to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

We reverse this rejection.

DISCUSSION

In reaching our decision in this appeal, we have given consideration to the appellants' specification and claims, and to the respective positions articulated by the appellants and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellants regarding the noted rejection, we make reference to the examiner's Answer for the examiner's reasoning in support of the rejection, and to the appellants' Brief and Reply Brief for the appellants' arguments thereagainst. As a consequence of our review, we make the determinations which follow.

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[1] An $F(ab')_2$ fragment is a fragment of an antibody containing two antigen binding sites generated by cleavage of the antibody molecule with the enzyme pepsin which cuts the hinge region C-terminally to the inter–chain disulphide bond.

35 U.S.C. § 112, first paragraph

Claims 30-49 stand rejected under 35 U.S.C. § 112, first paragraph for lack of written description and failing to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The examiner argues (Answer, pages 4-5):

> There is no support in the specification as originally filed for the recitation of "antibody fragment" in claims 30, 35, 40 or 45. The scope of the term "antibody fragment" encompasses compositions containing fragments not disclosed in the specification (eg. such as Fv or Fd or $F(ab)_2$). There is no written description in the specification as originally filed of the claimed conjugate or composition containing said conjugate wherein the conjugate contains a "antibody fragment" per se. ... There is also no support in the specification as originally filed for the recitation of "$F(ab')_2$" in claims 34, 39, 44 and 49. The specification pages 11 and 12, discloses the use of Fab' derived from $F(ab')_2$ for the preparation of the claimed invention, but there is no disclosure of the use of $F(ab')_2$ in the claimed invention. The specification merely discloses the use of $F(ab')_2$ to prepare Fab', wherein the Fab' are then used in the claimed invention. ... There is no written description in the specification as originally filed of the claimed invention (eg. the claimed invention constitutes new matter).

The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1116-17 (Fed. Cir. 1991) and In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983). Furthermore, claim language must be analyzed "not in a

vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary skill in the pertinent art." In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971). [Emphasis added.]

Our reviewing court has held in Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991) that:

> [a] fairly uniform standard for determining compliance with the "written description" requirement has been maintained throughout: "Although [the applicant] does not have to describe exactly the subject matter claimed, ... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (citations omitted). "[T]he test for sufficiency of support in a parent application is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.'" Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

Appellants argue that the subject matter of the claims need not be literally supported in the specification to meet the written description requirement. Brief, page 6.

Appellants argue (Brief, page 6):

> Applicants believe that the specification clearly teaches one skilled in the art how to use the claimed antibody fragments, such as Fab'. Further, Applicants also strongly believe that it is well known to one skilled in the art how to use other antibody fragments, such as $F(ab')_2$ in view of the state of the art at the time of the priority date of the present application.

Appellants further argue (Brief, page 7):

> It is appropriate for the claims to utilize claim language which does not readily appear in the specification as long as one skilled in the art would ***impliedly*** or ***inherently*** recognize that the applicant has invented the specific subject matter claimed. In reviewing the teachings of the specification set forth on pages 1, 3, 12, 36, 37 and 41, it is clear that the inventors did contemplate a pharmaceutical composition or a liposome/antibody conjugate comprising an antibody fragment of the monoclonal antibody.

Appellants submit that the "gist of the present invention resides in the finding of a specific monoclonal antibody defined by the amino acid sequences listed in the Sequence Listing, which can actually bind to the aimed antigen, and not in the finding that antibody fragments can also be used in the same manner as the antibodies themselves for the purpose of the invention. In other words, it not necessary under U.S. practice for the present application to teach what is widely known or recognized by those skilled in the art as of the priority date of the application. Since it is well known to one skilled in the art that antibody fragments in the field of 'targeting therapy' are used in the same manner as the antibody themselves, it clearly shows that the inventors contemplated the use of such fragments, as well as the antibodies themselves in the field of 'targeting therapy'". Brief, pages 8-9.

Appellants proffer three references, which teach the preparation and/or usefulness of antibody fragments in "targeting therapy". In particular, Wright describes the covalent linking of Fab' antibody to liposomes and their use as drug delivery vehicles. Wright, pages 350-351. Singhal describes the preparation and interactions

of anti-rat erythrocyte $F(ab')_2$-coupled liposomes with erythrocytes in whole blood. Singhal, page 72-74. Traut describes the reagents and methods used in cross-linking, using thiolation, of a protein having no thiol group. Brief, page 7. Thus, appellants argue that the state of the art generally provides those of ordinary skill in the art an indication that it is customary and routine to make and use antibody fragments, such as Fab' and $F(ab')_2$ in targeting therapies.

The examiner responds, arguing, "[r]egarding appellants comments in pages 8 and 9 of the instant Brief, appellants are arguing why the instant invention is obvious in view of the specification and prior art. There is no disclosure in the specification of the term 'antibody fragment'. There is no disclosure in the specification of the use of $F(ab')_2$ in the claimed invention. Appellants arguments are essentially drawn to the issue of why the claimed invention is obvious based on the disclosure of the specification and prior art." Answer, page 7. The examiner relies on the legal precedent of Lockwood v. American Airlines Inc., 107 F.3d 1565, 1571-1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997), for the proposition that the written description of an invention extends only to that which is disclosed in the prior application, and does not extend to subject matter which is not disclosed, but what is obvious in view of what is expressly disclosed. Answer, pages 7-8.

We do not agree with the examiner that the facts of the case before us suggest an attempt of appellants to claim what is obvious in view of what is expressly disclosed in the specification, as in Lockwood.

The written description requirement serves "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material." In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). In order to meet the written description requirement, the appellants do not have to utilize any particular form of disclosure to describe the subject matter claimed, but "the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Put another way, "the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Finally, "[p]recisely how close the original description must come to comply with the description requirement of section 112 must be determined on a case-by-case basis." Eiselstein v. Frank, 52 F.3d 1035, 1039, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) (quoting Vas-Cath, 935 F.2d at 1561, 19 USPQ2d at 1116).

Upon review of the specification as filed, in our view, the specification, when read in the eyes of one of ordinary skill in the art, as evidenced by Wright and Singhal, provides a sufficient description to allow persons of ordinary skill in the art to recognize that appellants invented what is claimed, antibody fragments including Fab' and $F(ab')_2$. While the examiner is correct in that the claim terminology "antibody fragment" does not literally appear in the specification as filed, the originally filed specification does

describe the use of Fab' antibody fragments within the scope of the invention. For example, the originally filed claims in the application recited an "antibody", and interestingly the only working example in the specification used antibody fragments (Fab'). Specification, page 36, et. seq. Moreover, this working example is entitled, "Preparation of Adriamycin-Containing Liposome Bonded to Antibody GAH." Thus, the working example in the specification reasonably supports appellants' argument that the term "antibody" in the specification is used generically to include fragments with the same antigen-binding activity.

The specification makes clear that the inventive aspect of the disclosure was the antigen-specific domains defined by the specific variable light and heavy chain regions recited in the claimed SEQ ID's. One of ordinary skill in the art would have understood appellants to have invented not just the full-length antibodies including these specific sequences but all fragments thereof comprising the antigen specific domains of the antibody. In our view, appellants' prior art evidences that one of ordinary skill in the art would have understood appellants' disclosure to encompass liposome targeting with fragments of antibodies as well as full length antibodies.

The specification also describes the use of $F(ab')_2$ to prepare the Fab' antibody fragments for use in the claimed invention. It would reasonably appear, taking into consideration the state of the art at the time of the invention, that persons of ordinary skill in the art would understand that $F(ab')_2$ antibody fragments mentioned in the specification could be bound to liposomes, and could also be used to prepare a

pharmaceutical composition, as claimed. The rejection of the claims for lack of written description of the term "antibody fragments" is reversed.

CONCLUSION

The rejection of claims 30-49 under 35 U.S.C. § 112, first paragraph, for lack of written description is reversed.

REVERSED

SHERMAN D. WINTERS)
Administrative Patent Judge)
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DEMETRA J. MILLS) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
) INTERFERENCES
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